Preface

Cardiac arrhythmias, such as ventricular tachycardia (VT) and ventricular fibrillation (VF), are among the leading causes of death in the industrialized world. There is growing consensus that these arrhythmias are associated with the formation of spiral and scroll waves of electrical activation in mammalian cardiac tissue; whereas single spiral and scroll waves are believed to be associated with VT, their turbulent analogs are associated with VF. Thus, the study of these waves is an important biophysical problem in-so-far-as to develop an understanding of the electrophysiological basis of VT and VF.

In this thesis, we provide a brief overview of recent numerical studies of spiral- and scroll-wave dynamics in mathematical models of mammalian cardiac tissue. In addition to giving a description of how spiral and scroll waves can be initiated in such models, how they evolve, how they interact with conduction and ionic inhomogeneities, how their dynamics is influenced by the size and geometry of the heart, we also discuss how active Purkinje networks and passive fibroblast clusters modify the electrical activity of cardiomyocytes, and the relevance of such studies to defibrillation.

In **Chapter** 2 we present a systematic study of the combined effects of muscle-fiber rotation and inhomogeneities on scroll-wave dynamics in the TNNP (ten Tusscher Noble Noble Panfilov) model for human cardiac tissue. In particular, we use the three-dimensional (3D) TNNP model with fiber rotation and consider both conduction and ionic inhomogeneities. We find that, in addition to displaying a sensitive dependence on the positions, sizes, and types of inhomogeneities, scroll-wave dynamics also depends delicately upon the degree of fiber rotation. We find that the tendency of scroll waves to anchor to cylindrical conduction inhomogeneities increases with the radius of the inhomogeneity. Furthermore, the filament of the scroll wave can exhibit drift or meandering, transmural bending, twisting, and break-up. If the scroll-wave filament exhibits weak meandering, then there is a fine balance between the anchoring of this wave at the inhomogeneity and a disruption of wave-pinning by fiber rotation. If this filament displays strong meandering, then again the anchoring is suppressed by fiber rotation; also, the scroll wave can be eliminated from most of the layers only to be regenerated by a seed wave. Ionic inhomogeneities can also lead to an anchoring of the scroll wave; scroll waves can now enter the region inside an ionic inhomogeneity and can display a coexistence of spatiotemporal chaos and quasi-periodic behavior in different parts of the simulation domain. We discuss the experimental implications of our study.

In **Chapter** 3 we present a comprehensive numerical study of plane and scroll waves of electrical activation in two state-of-the-art ionic models for rabbit and pig cardiac

tissue. We use anatomically realistic, 3D simulation domains, account for muscle-fiber rotation, and show how to include conduction and ionic inhomogeneities in these models; we consider both localized and randomly distributed inhomogeneities. Our study allows us to compare scroll-wave dynamics, with and without inhomogeneities, in these rabbit- and pig-heart models at a level that has not been attempted hitherto. We begin with a comparison of single-cell action potentials (APs) and ionic currents in the Bers-Puglisi (BP) and modified-Luo-Rudy I (mLRI) models for rabbit- and pig-myocytes, respectively. We then show how, for plane-wave propagation in rabbit- and pig-heart models, the conduction velocity CV and wavelength λ depend on the distance of the plane of measurement from the plane containing the heart apex. Without inhomogeneities, and in the parameter régime in which these models display scroll waves, the rabbit-heart model supports a single scroll wave, which rotates periodically, whereas the pig-heart model supports two scroll waves, which rotate periodically, but with a slight difference in phase; this is partly because the rabbit-heart model is smaller in size, than the pig-heart one. With randomly-distributed inhomogeneities, we find that the rabbit-heart model loses its ability to support electrical activity, even at inhomogeneity concentrations as low as 5%. In the pig-heart model, we obtain rich, scroll-wave dynamics in the presence of localized or distributed inhomogeneities, both of conduction and ionic types; often, but not always, scroll waves get anchored to localized inhomogeneities; and distributed inhomogeneities can lead to scroll-wave break up.

In **Chapter** 4, we present a comprehensive numerical study of spiral-and scroll-wave dynamics in a state-of-the-art mathematical model for human ventricular tissue with fiber rotation, transmural heterogeneity, myocytes, and fibroblasts. Our mathematical model introduces fibroblasts randomly, to mimic diffuse fibrosis, in the ten Tusscher-Noble-Noble-Panfilov (TNNP) model for human ventricular tissue; the passive fibroblasts in our model do not exhibit an action potential in the absence of coupling with myocytes; and we allow for a coupling between nearby myocytes and fibroblasts. Our study of a single myocyte-fibroblast (MF) composite, with a single myocyte coupled to N_f fibroblasts via a gap-junctional conductance G_{gap}, reveals five qualitatively different responses for this composite. Our investigations of two-dimensional domains with a random distribution of fibroblasts in a myocyte background reveal that, as the percentage P_f of fibroblasts increases, the conduction velocity of a plane wave decreases until there is conduction failure. If we consider spiral-wave dynamics in such a medium we find, in two dimensions, a variety of nonequilibrium states, temporally periodic, quasiperiodic, chaotic, and quiescent, and an intricate sequence of transitions between them; we also study the analogous sequence of transitions for three-dimensional scroll waves in a three-dimensional version of our mathematical model that includes both fiber rotation and transmural heterogeneity. We thus elucidate random-fibrosis-induced nonequilibrium transitions, which lead to conduction block for spiral waves in two dimensions and scroll waves in three dimensions. We explore possible experimental implications of our mathematical and numerical studies for plane-, spiral-, and scroll-wave dynamics in cardiac tissue with fibrosis.

In **Chapter** 5 we present a detailed numerical study of the electrophysiological interactions between a random Purkinje network and simulated human endocardial tissue, (a) in the presence of, and (b) in the absence of existing electrical excitation in the system. We study the dependence of the activation-onset-time (t_a) on the strength of coupling (D_{mp}) between the myocyte layer and the Purkinje network, in the absence of any external stimulus. Since the connection between the endocardial layer and the Purkinje network occurs only at discrete points, we also study the dependence of t_a on the number of Purkinje-myocyte junctions (PMJs) at fixed values of D_{mp}, in the absence of any applied excitation. We study signal propagation in the system; our results demonstrate the situations of (a) conduction block from the Purkinje layer to the endocardial layer, (b) anterograde propagation of the excitation from the Purkinje layer to the endocardium, (c) retrograde propagation of the excitation from the endocardium to the Purkinje layer and (d) development of reentrant circuits in the Purkinje layer that lead to formation of ectopic foci at select PMJs. We extend our study to explore the effects of Purkinje-myocyte coupling on spiral wave dynamics, whereby, we find that such coupling can lead to the distortion and breakage of the parent rotor into multiple rotors within the system; with or without internal coherence. We note that retrograde propagation leads to the development of reentrant circuits in the Purkinje network that help to initiate and stabilize ectopic foci. However, in some cases, Purkinje-myocyte coupling can also lead to the suppression of spiral waves. Finally we conduct four representative simulations to study the effects of transmural heterogeneity, fiber rotation and coupling with a non-penetrating Purkinje network on a three dimensional slab of cardiac tissue.

Lastly, In **Chapter** 6, we study reentry associated with inexcitable obstacles in the ionically-realistic $TNNP$ model for human ventricular tissue, under the influence of high-frequency stimulation. When a train of plane waves successively impinge upon an obstacle, the obstacle splits these waves as they tend to propagate past it; the emergent broken waves can either travel towards each other, bridging the gap introduced by the obstacle at the time of splitting, or, they can travel away from each other, resulting in the growth of the gap. The second possibility eventually results in the formation of spiral waves. This phenomenon depends on frequency of the waves. At high frequency, the excitability of the tissue decreases and the broken waves have a tendency to move apart. Hence high-frequency stimulation increases the chances of reentry in cardiac tissue. We correlate the critical period of pacing that leads to reentry in the presence of an inexcitable obstacle, with the period of spiral waves, formed in the homogeneous domain, and study how the critical period of pacing depends on the parameters of the model.

References

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